

Attorney Docket No.: **ISPH-0524**
Inventors: **Bennett et al.**
Serial No.: **09/734,847**
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REMARKS

Claims 34-63 are pending in the instant application. Claims 34-63 have been rejected. Claims 34, 57 and 63 have been amended. No new matter has been added by these amendments to the claims. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Rejection of Claims Under 35 U.S.C. 103(a)

Claims 34, 35, 38-43, 48, 49, 53, 56 and 57 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. (WO 95/04748 A1), in view of Burchardt et al. (US Patent 6,395,474 B1). The Examiner suggests that it would have been *prima facie* obvious for one of ordinary skill in the art to modify the teachings of Anderson et al. (Peptide nucleic acid oligomers targeting mRNA sequences to control mRNA stability and processing, including those targeted to the 5'CAP, intron/exon junctions, and the 5'-UTR) with the modifications taught by Burchardt et al. (Modifying peptide nucleic acids by attaching ligand to either terminus, including terminal lysine modifications) to design the method of the instant invention. The Examiner suggests that one would be motivated to modify the

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oligomers of Anderson et al. with the lysine modifications of Burchardt et al. because the modification is disclosed to strengthen the binding of P.A. oligomers to their target nucleic acid. Although the teachings of Anderson et al. do not explicitly teach a method of modulating splicing, absent evidence to the contrary, it would be expected. Further, the Examiner suggests that the references teach targeting wild-type mRNAs since statements in the references are not limiting to only viral mRNAs. Applicants respectfully traverse this rejection.

Anderson et al. disclose methods of modulating viral processes, specifically in cytomegalovirus and papillomavirus. Although this patent discloses peptide nucleic acid oligomers targeting mRNA sequences that control mRNA stability and processing in viral cells, nowhere does this patent teach a method of modulating processing of wild-type cellular mRNA targets as claimed. Nowhere does the patent define mRNAs to include specifically wild-type mRNAs. Therefore, this patent fails to teach the limitations of the instant invention, which are modulation of processing of wild-type cellular mRNA, not viral mRNA as taught by Anderson et al.

The secondary reference cited by the Examiner fails to overcome the deficiencies in teaching of this primary reference.

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Buchardt et al. disclose that binding of peptide nucleic acid oligomers may be modulating through attachment of ligands to the terminus of a peptide nucleic acid. However, nowhere does this patent teach a specific method of modulating processing of wild-type cellular mRNA as claimed.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. The limitations of the claims as amended, which specify methods for modulating processing of wild-type cellular mRNA, are not taught or suggested by the references individually or when combined. Therefore, the limitations of the claims as amended clearly are not taught or suggested by the combination of prior art references, nor is any expectation of successful development of method such as claimed. It is only with the specification in hand that one of skill would understand that the method of the instant invention was a viable method for modulating processing of wild-type cellular mRNA. Further, the

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cited art fails to provide one of skill with the motivation to design such a method as the prior art cited focuses on viral cell mRNA processing and drugs to treat viral infections. Thus, the combination of prior art cited cannot render the instant claimed invention obvious. However, in an earnest effort to advance the prosecution of this case, Applicants have further amended the claims to remove reference to peptide nucleic acids. Accordingly, these references fail to teach the limitations of the claims as now amended and withdrawal of this rejection is therefore respectfully requested.

II. Rejection of Claims Under 35 U.S.C. 112, First Paragraph

Claims 34-63 have been rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The Examiner acknowledges that the specification is enabling for practice of the claimed method *in vitro* but suggests that *in vivo* practice for therapeutic treatment is not enabled. Applicants respectfully traverse this rejection.

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Applicants disagree with the Examiner's suggestion that cited references on antisense technology support the position that application of antisense *in vivo* is unpredictable.

As discussed in the previous response, the Examiner has pointed to articles on the technology of antisense oligonucleotides to support the view that antisense technology is unpredictable. However, when one reads each of these papers as a whole, as required under MPEP 2141.02, these references actually teach the potential usefulness of this class of drugs in humans, and more importantly fail to provide any reasonable basis to doubt the pharmacological activity observed in cells in the instant invention would also occur in cells in animals and humans.

The paper by Branch (1998) is cited by the Examiner in support of her position. This paper teaches the need to develop antisense molecules based on sound data and careful screening, such as is presented in the instant specification. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects in humans is unpredictable. The Examiner, however, attempts to use this paper to support suggestions concerning the inaccessibility of most potential target RNA binding sites to antisense molecules and the unpredictability of antisense

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effects. One of skill in the art would not expect to predict the "winning" antisense compound *a priori*, but would screen a reasonable number of compounds in order to find the one best suited to his or her needs. Time and difficulty of experiments are not determinative of enablement if they are merely routine. Quantity of examples is only one factor that must be considered before reaching the final conclusion that undue experimentation would be required. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. (MPEP 2164.06). The fact that effective antisense drugs are selected from large pools of candidates and then optimized, rather than predicted *a priori*, does not indicate lack of enablement, i.e., the need for undue experimentation. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

The paper of Jen et al. (2000) is cited by the Examiner as discussing the challenges that remain in the use of antisense

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before it becomes routine. However, again, this paper is not stating that results of well-designed *in vitro* studies would not provide one of skill in the art with assurance that *in vivo* activity is likely with a compound shown to have activity *in vitro*.

The paper by Crooke is a review paper on the basic principles of antisense therapeutics. The statements alluded to by the Examiner concerning extrapolations from *in vitro* uptake studies to predictions about *in vivo* pharmacokinetic behavior are only one small part of this review paper. When read in its entirety the author is merely stating a well known fact in the development of any drug, not merely antisense. Pharmacokinetics is not the study of the pharmacological activity of an agent, such as is studied commonly in cells, but rather the study of the biological distribution of a drug in an animal or human. Therefore, the statements by the author do not demonstrate the unpredictability of antisense oligos *in vivo* but rather merely state the obvious, that one would not use studies on cellular uptake to predict pharmacokinetics in animals or humans because it is not a logical use of such data for any drug. Data in cells are used routinely, however, as predictors of pharmacological

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activity in animals and humans. It is a fundamental principle of drug development that data from whole cell studies, such as are provided in the instant specification, are directly applicable to predicting *in vivo* activity. The teachings of the paper by Crooke and the other cited review paper (Branch) provide no reason to doubt that this fundamental principle is applicable to antisense agents.

In fact, statements in the paper by Crooke support the fact that development of antisense drug products is viewed by those of skill in the art as being the same as development of any other drug product in terms of applying the basic principles of pharmacology. For example, on page 22, first paragraph, Crooke points out "...numerous well-controlled [pharmacological] studies have been reported in which antisense activity was conclusively demonstrated [*in vitro*]." The key according to Crooke is the careful design of the *in vitro* studies to carefully evaluate dose-response relationships and antisense mechanism, similar to the type of studies presented in the instant specification. Therefore, what this paper, and the other cited by the Examiner actually teach is that antisense oligonucleotides must be developed using well designed studies that progress logically from activity in cells to activity in animals and humans.

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Nowhere in the reference does the author state or suggest that results of well-designed *in vitro* pharmacological studies would not be predictive of activity *in vivo*.

It must also be remembered that demonstration of therapeutic activity is not a requirement of patentability. The case law is clear; Applicants do not have to provide actual evidence of success in treating humans where such a utility is asserted. If one skilled in art would accept the data provided as being reasonably predictive of utility in humans, evidence from such tests should be considered sufficient to support credibility of the asserted utility. *In re Hartop*, 311 F.2d 249, 135 USPQ 419 (CCPA 1962); *In re Krimmel*, 292 F.2d 948, 953, 130 USPQ 215, 219 (CCPA 1961); *Ex parte Krepelka*, 231 USPQ 746 (Bd. Pat. App. & Inter. 1986).

Further, Applicants point the Examiner to a paper in the published literature (Lu, Q.L. et al. 2003, Nature Med. 9:1009-1014) where *in vivo* data is provided showing that redirection of splicing in dystrophic mice using antisense oligonucleotides is able to restore function in the animals *in vivo*. Thus, this data provides the Examiner with further proof of the successful use of antisense compounds *in vivo*, in this case in an

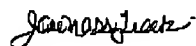
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application that is directly relevant to the claimed invention. Accordingly, based on this data and what is generally known to one of skill in the art of antisense, Applicants believe that the specification supports the use of the invention as claimed. Withdrawal of this rejection is respectfully requested.

III. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,



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Date: December 15, 2004

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